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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/487,841	01/19/2000	Roy A. Gravel	50004/003004	3640

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EXAMINER	
CHEN, SHIN LIN	
ART UNIT	**PAPER NUMBER**
1632	

DATE MAILED: 11/20/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/487,841	GRAVEL ET AL.	
	Examiner	Art Unit	
	Shin-Lin Chen	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 August 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *6-9,11-21 and 35-43* is/are pending in the application.

4a) Of the above claim(s) *12 and 15-20* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *6-9,11,13,14,21 and 35-43* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 8-18-03 has been entered.

Claims 1-3, 5, 10 and 22-34 have been canceled. Claim 6 has been amended. Claims 35-43 have been added. Claims 6-9, 11-21 and 35-43 are pending. Claims 12 and 15-20 are withdrawn from consideration. Claims 6-9, 11, 13, 14, 21 and 35-43 are under consideration.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 6-9, 11, 13, 14, 21 and 35-43 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for increased risk for mothers to develop neural tube defects (NTD) with combination of homozygous mutant MTRR genotype having an A/G polymorphism at base 66, which yields an isoleucine (22I) or a methionine (22M) at amino acid position 22, and low cobalamin; increased risk to develop NTD when case mother or case child has both homozygous MTRR 66 A/G mutation and homozygous methylenetetrahydrofolate reductase (MTHFR) 677 C/T mutation (SEQ ID No. 51); mothers of Down's Syndrome babies are more likely to have homozygous MTRR polymorphism of A->G at nucleotide position 66

and MTHFR polymorphism C->T at nucleotide position 677 than control mothers; and individuals having a MTRR homozygous 66 A->G polymorphism are at greatest risk of developing coronary artery disease (CAD) and the association of the MTRR genotype with CAD is not modulated by vitamin B12 status or MTHFR genotype (See specification page 56, 58, 59, 63, 66, 68), does not reasonably provide enablement for a method for detecting an increased risk of developing a NTD, Down's Syndrome, hyperhomocysteinmia, cancer or cardiovascular disease in any mammalian fetus or embryo by detecting any heterozygous or homozygous MTRR polymorphism in either or both future parents of said embryo or fetus, or in said embryo or fetus. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Claims 6-9, 11, 13, 14, 21, 36, 38 and 40 are directed to a method for detecting an increased risk of developing a NTD, Down's Syndrome, or cardiovascular disease in any mammalian fetus or embryo by detecting any heterozygous or homozygous MTRR polymorphism as recited in the claims in either or both future parents of said embryo or fetus, or in said embryo or fetus. Claim 21 specifies the cardiovascular disease is a premature coronary artery disease. Claim 38 further comprises measuring the level of cobalamin in the test subject. Claims 35, 37, 39 and 41-43 are directed to a method for detecting an increased risk of developing Down's Syndrome, hyperhomocysteinemia, cardiovascular disease, or cancer in a mammal by detecting the presence of a homozygous MTRR polymorphism as recited in the claims. Claim 43 specifies the cardiovascular disease is a premature coronary artery disease. Claim 39 further comprises measuring the level of cobalamin in the mammal.

The specification of the present application discloses increased risk for mothers to develop neural tube defects (NTD) with combination of **homozygous** mutant MTRR genotype having an A/G polymorphism at base 66, which yields an isoleucine (22I) or a methionine (22M) respectively at amino acid position 22, and **low cobalamin level**; increased risk to develop NTD when case mother or case child has both **homozygous** MTRR 66 A/G mutation and **homozygous** MTHFR 677 C/T mutation; mothers of Down's syndrome babies are more likely to have **homozygous** MTRR polymorphism of A->G at nucleotide position 66 and homozygous MTHFR polymorphism C->T at nucleotide position 677 than control mothers; and individuals having a MTRR **homozygous** 66 A->G polymorphism are at greatest risk of developing coronary artery disease (CAD) and the association of the MTRR genotype with CAD is not modulated by vitamin B12 status or MTHFR genotype (See specification page 56, 58, 59, 63, 66, 68). The claims encompass detecting an increased risk of developing the disease set forth above by detecting any heterozygous or homozygous MTRR polymorphism.

The specification fails to provide adequate guidance and evidences for any polymorphism or mutation within the MTRR gene other than the polymorphism disclosed in the specification and fails to teach the correlation of said MTRR polymorphism or mutation with increased risk of developing a NTD, Down's Syndrome, or cardiovascular disease in any mammalian fetus or embryo, or with increased risk of developing Down's Syndrome, hyperhomocysteinemia, cardiovascular disease, or cancer in a mammal.

It was known in the art that different polymorphism or mutation within a gene could result in dramatic different effect on the function of the gene product and NTD, Down's Syndrome, hyperhomocysteinemia, cancer and cardiovascular disease are different diseases that

differ pathologically and differ in their mechanisms in developing those diseases. Therefore, different MTRR polymorphism or mutation would have different correlations with increased risk of developing a NTD, Down's Syndrome, hyperhomocysteinemia, cancer, or cardiovascular disease. Ferenci, 2003 (Gut, Vol. 52, suppl 2, ii6-9) states that "The application of molecular genetics in everyday clinical routine is hampered by the difficult interpretation of test results. These difficulties include the prediction of disease penetrance, the presence of multiple mutations of a particular gene with varying functional consequences, and the importance of exogenous factors modulating disease expression" (e.g. abstract). The mutations include gain of function and loss of function mutations and mutations that result in less pronounced functional consequences. "The mutation may affect the tertiary structure of the gene product, its assembly, inactivation, secretion, or conformational stability" (bridging p. ii6, ii7). "The difficulties of understanding the role of mutation can be best described in cystic fibrosis (CF). Today more than 850 mutations of the CFTR gene were reported. Some mutations like the deltaF508 mutation are common and account for more than 70% of cases of clinically overt CF. Other mutations are rare and occur sometimes in single families" (e.g. p. ii7, left column). Walon et al., 1997 (Human Genetics, Vol. 100, p. 601-605) reports that 23 germline mutations have been identified in APC gene and only in two instances a clear cut genotype-phenotype correlation is observed. "Our data illustrate the wide genetic and phenotypic heterogeneity of this condition between and within the families, making the establishment of correlations complex and any prediction in this disease difficult, although targeting the mutation site may be helpful in some specific cases" (e.g. abstract). Therefore, it was difficult to predict the resulting phenotype from various mutations of a gene and it was unpredictable at the time of the invention whether a

mutation or polymorphism of MTRR or in combination with other gene mutation, such as MTHFR mutation or polymorphism, or other factor would increase the risk of developing NTD, Down's Syndrome, hyperhomocysteinemia, cardiovascular disease, or cancer in a mammal or a fetus or an embryo.

Further, the specification of the present application discloses that no increased risk of developing NTD could be correlated to a mother or child having homozygous MTRR 22M polymorphism (specification, bridging p. 57-58) and no correlation of increased risk of developing a NTD, Down's Syndrome, cancer, or cardiovascular disease with heterozygous or homozygous MTRR G/A polymorphism at nucleotide position 110, with a deletion of 4 nucleotides at 1675-1678 of MTRR or deletion of 3 nucleotides at 1726-1728 of MTRR, or with heterozygous MTRR 22IM polymorphism has been disclosed.

The specification indicates that mother or child homozygous MTRR 22M polymorphism (66 A/G) does not have significant effect in increasing risk of developing NTD (bridging p. 57-58). The specification fails to provide evidence for the correlation between MTRR polymorphism alone with an increased risk of developing any NTD, Down's Syndrome, hyperhomocysteinemia, or cancer in a mammal. There is no evidence of record that any heterozygous MTRR polymorphism or heterozygous MTHFR polymorphism or combination of both has any correlation with increased risk of developing any NTD, Down's Syndrome, hyperhomocysteinemia, cardiovascular disease, or cancer in a mammal. The specification only reports the detection of a 4 bp deletion, 1675del4, in WG788 cell line, and a 3 bp deletion, 1726delTTG, in WG1836 cell line but fails to correlate these mutation with increased risk of

developing any NTD, Down's Syndrome, hyperhomocysteinemia, cardiovascular disease, or cancer in a mammal (see p. 54, 55).

In view of the evidence and reasons set forth above, it was unpredictable at the time of the invention whether a polymorphism or a mutation within MTRR gene either heterozygous or homozygous would be correlated to increased risk of developing a NTD, Down's Syndrome, hyperhomocysteinmia, cancer, or cardiovascular disease in a mammal or a fetus or an embryo, and one skilled in the art at the time of the invention would not be able to predict whether a test subject would have increased risk of developing said diseases by detecting any heterozygous or homozygous polymorphism or mutation within MTRR gene in said test subject.

Therefore, it is concluded that based upon the nature of the claimed invention, the state of the art, the unpredictability found in the art, the teaching and working examples provided, and the breadth of the claims that it would require one skilled in the art at the time of the invention undue experimentation to practice over the full scope of the invention claimed.

Applicants cite specification pages 2, 4 and 32 and argue that the polymorphisms in the human MTRR gene correlate with an increased risk of hyperhomocysteinemia, cardiovascular disease, NTD, cancer, and Down's syndrome, and the specification teaches standard method of identifying polymorphism of MTRR gene (amendment, p. 7-8). This is not found persuasive because of the reasons set forth above under 35 U.S.C. 112 first paragraph rejection. The MTRR gene polymorphism is considered in the claims but not the methionine synthase gene. The specification only indicates that the presence of mutations in MTRR gene **are likely** to be associated with altered risk for cardiovascular disease, neural tube defects, and cancer. There is no evidence of record that the mutations recited in the claims are correlated to the increased risk

of developing those diseases. It appears that further study is required to confirm the correlation between the MTRR mutations and increased risk of developing the diseases recited in the claims. The method of identifying the MTRR polymorphisms is only a tool of identification but it is not necessary that the MTRR polymorphisms are correlated to increased risk of developing the diseases recited in the claims. The specification must provide sufficient enabling disclosure for the claimed invention but fails to do so. Thus, claims 6-9, 11, 13, 14, 21 and 35-43 are rejected under 35 U.S.C. 112 first paragraph.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shin-Lin Chen whose telephone number is (703) 305-1678. The examiner can normally be reached on Monday to Friday from 9:30 am to 6 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds can be reached on (703) 305-4051. The fax phone number for this group is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist, whose telephone number is (703) 308-0196.

S Chen

Shin-Lin Chen, Ph.D.